Phenylketonuria

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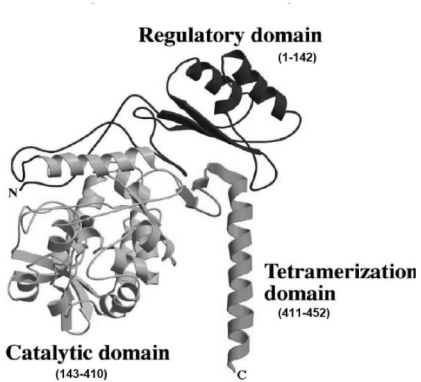
Service Learning Initiative in Biochemistry 5614 (Autumn 2019)



Domain structure of phenylalanine hydroxylase

Digital image retrieved Oct 14, 2019 from

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2423317/#b15-

History

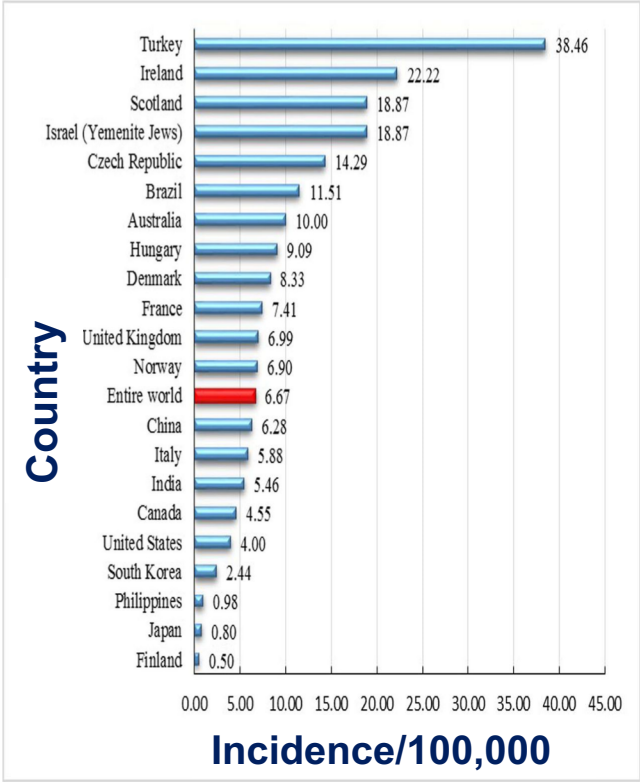
- Phenylketonuria (PKU) was discovered by Dr. Asbjørn Følling in the 1930s.
- A concerned mother brought in her two children to Dr. Følling after noticing a musty smell in their urine and mental decline during early childhood.
- Dr. Følling observed an unusually high level of phenylpyruvate in their urine, and concluded that the children could not properly metabolize the amino acid phenylalanine.

Dr. Asbjørn Følling

The discovery of phenylketonuria: The story of a young couple, two retarded children, and a scientist. Digital image retrieved Oct 28, 2019 from https://doi.org/10.1542/peds.105.1.89

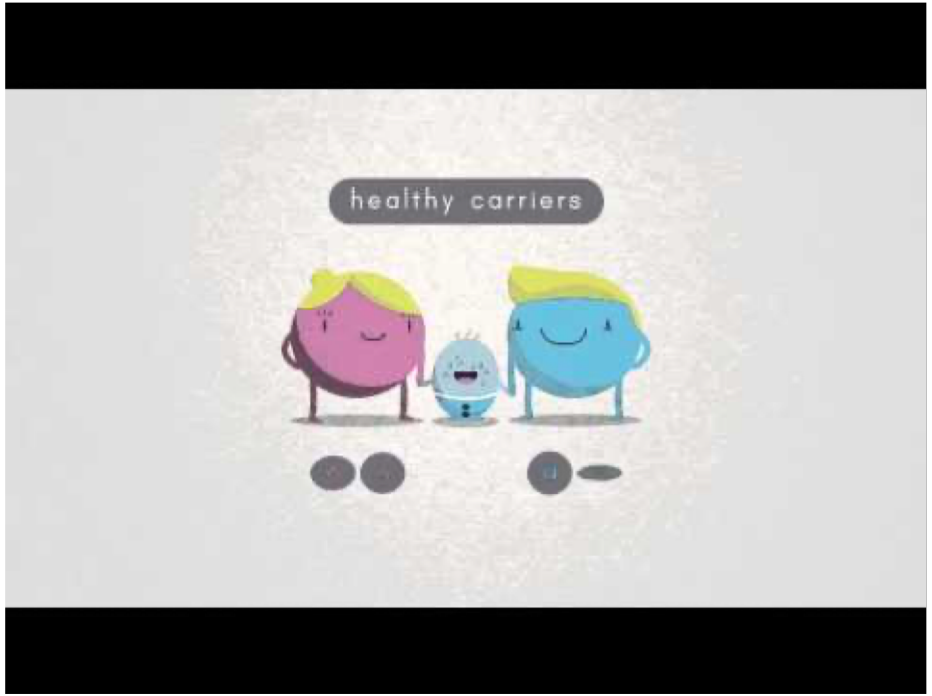
Occurrence, provenance, and genetics

- PKU is most prevalent in Turkey (1 in 2,500), as well as in Ireland, Scotland, and among Yemenite Jews (1 in 5,000)
- Mutation in the Phenylalanine Hydroxylase gene
- Autosomal recessive allele in chromosome 12



Phenylketonuria Incidence by country.
Digital image retrieved Oct 14, 2019 from
https://bmjopen.bmj.com/content/9/8/e031474#F3

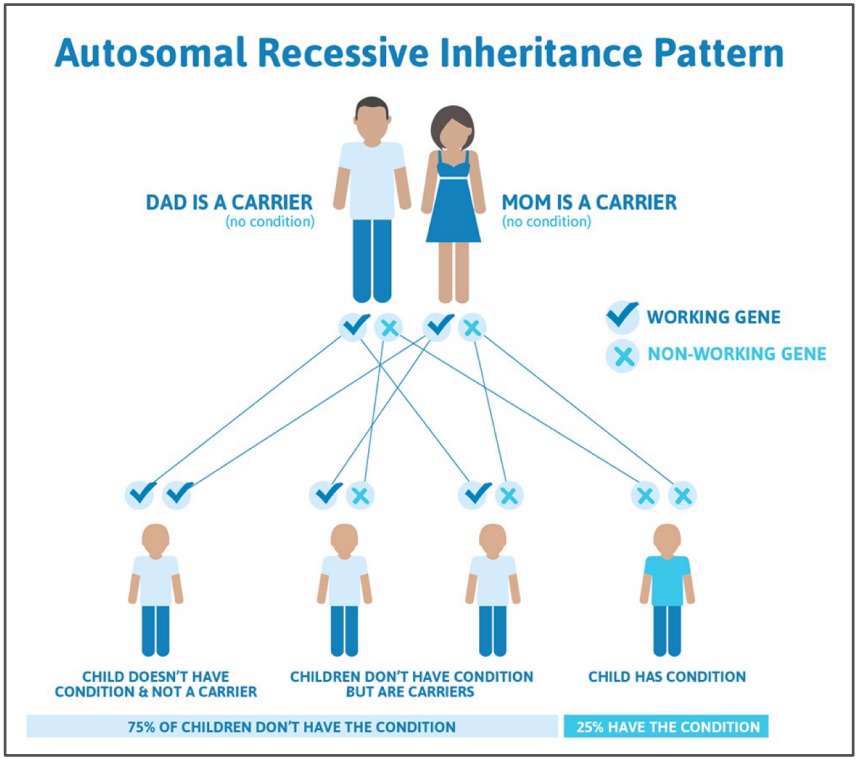
Autosomal recessive inheritance



Autosomal Recessive Inheritance - Genetics

Video file retrieved Jan 12, 2020 from

https://www.youtube.com/watch?time_continue=4&v=Nv6qUsKYodA&feature=emb_logo



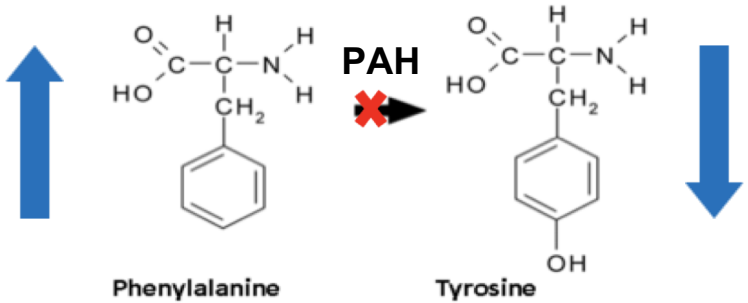
Autosomal Recessive Inheritance

Digital image retrieved Jan 12, 2020 from

https://www.geneticsupport.org/genetics-101/inheritance-patterns/autosomal-recessive/

Biochemical features

- Inability to properly metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine (Tyr) due to mutations in PAH.
- Both Phe and Tyr are essential for protein synthesis
  - Phe and Tyr are present in eggs, soybeans, meats, and other foods
- In PKU, there is a buildup of Phe, which disrupts brain function

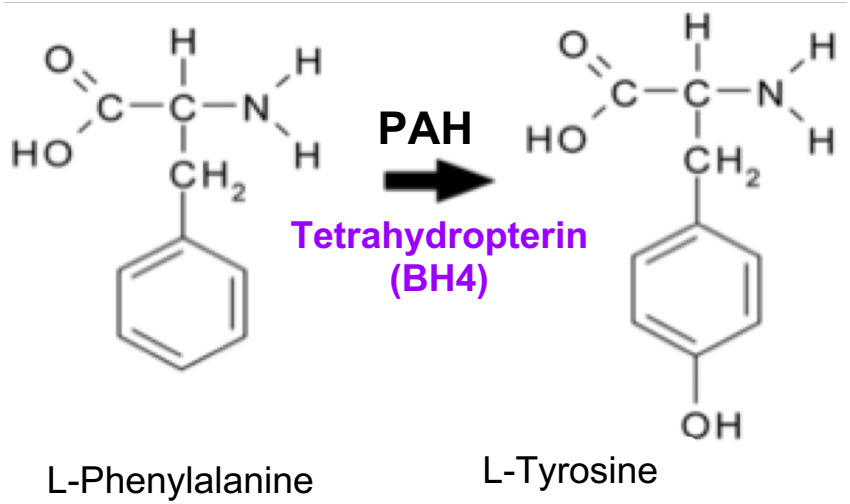


Structures of phenylalanine and tyrosine

Digital image retrieved Oct 28, 2019 from

https://lrodgers93.wordpress.com/2014/03/19/the-fate-of-phenylalanine/

Biochemical features



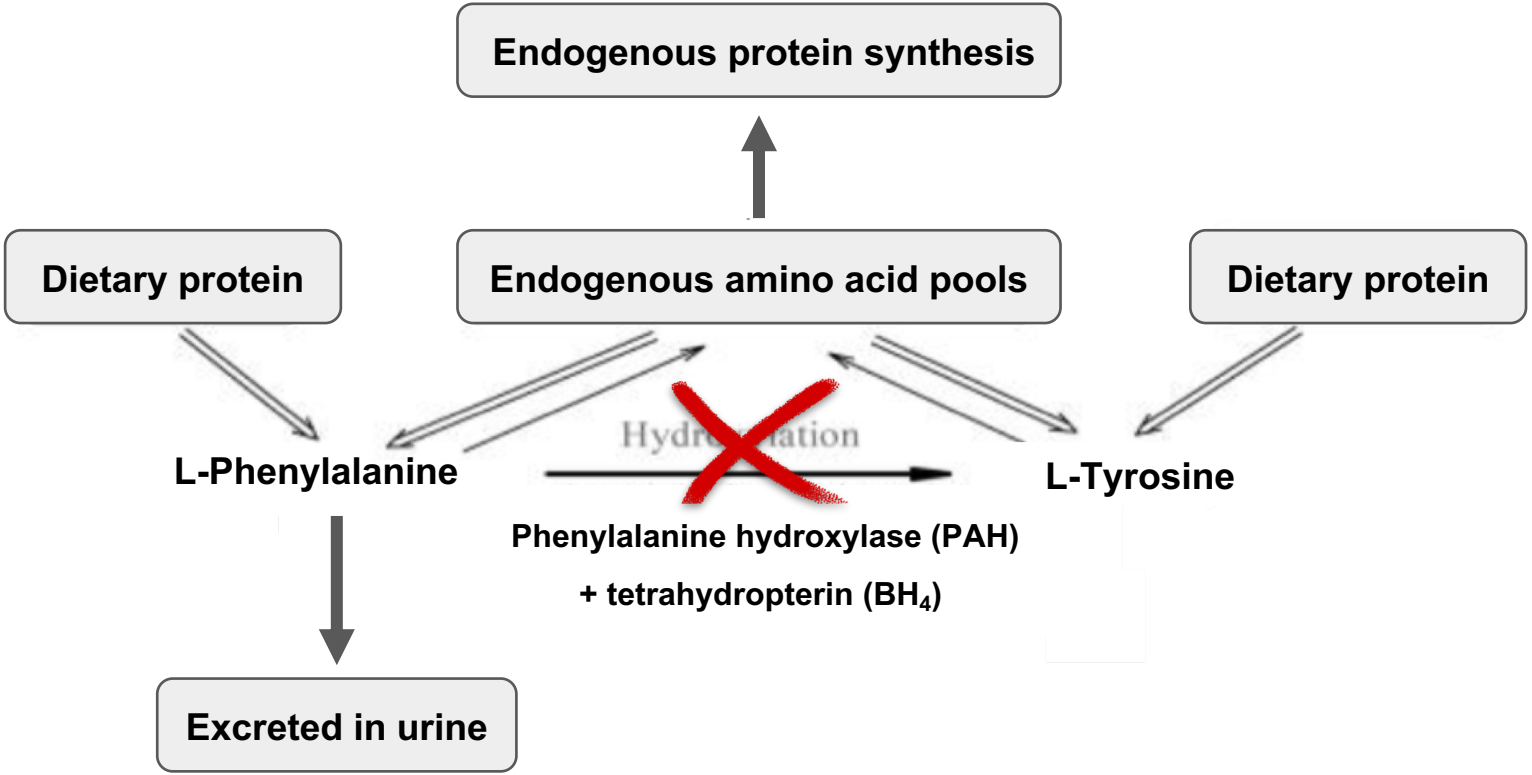
➢ BH4 is a coenzyme/cofactor that is necessary for PAH to convert Phe to Tyr.

Structures of phenylalanine and tyrosine

Digital image retrieved Oct 28, 2019 from

https://lrodgers93.wordpress.com/2014/03/19/the-fate-of-phenylalanine/

Biochemical features



Phe metabolism in humans

Digital image retrieved on Nov 10, 2019 from

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2423317/

Diagnosis

- PKU is detected via a newborn heel prick test
  - Only requires 4 drops of blood
  - Detects Phe elevation in blood

- If elevated Phe level is detected, newborn is treated immediately to avoid symptoms

Newborn blood spot screening

Digital image retrieved Oct 14, 2019 from

https://www.nhs.uk/conditions/pregnancy-and-baby/newborn-blood-spot-faqs/

Symptoms

Severe symptoms

- Progressive intellectual disability
- Delayed development (e.g., speech)
- Seizures
- Motor deficits

Mild symptoms

- Skin rashes
- Musty odor to urine
- Increased irritability which leads to loss of sleep

Symptoms do not show up in newborns but develop within a few months in the absence of treatment

Prognosis

- PKU does not affect life expectancy, with or without treatment
- Clinical severity depends on the degree of PAH deficiency

subtype	fold increase blood [Phe] (over normal)	clinical picture (brain dysfunction)	treatment required?
classic PKU (untreated)	>20	severe mental retardation	yes
mild PKU (untreated)	10-15	cognitive loss	yes
non-PKU mild HPA	2-8	normal	maybe

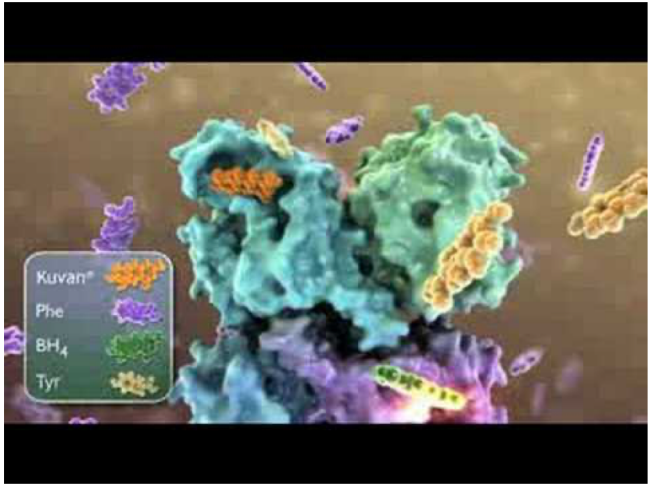
- Non-classical PKU individuals may not need treatment

Table above reproduced without modifications and retrieved Nov 15, 2019

https://www.ccrc.uga.edu/~steet/bcmb8160/lectures/PKU%20lecture.pdf

Therapy

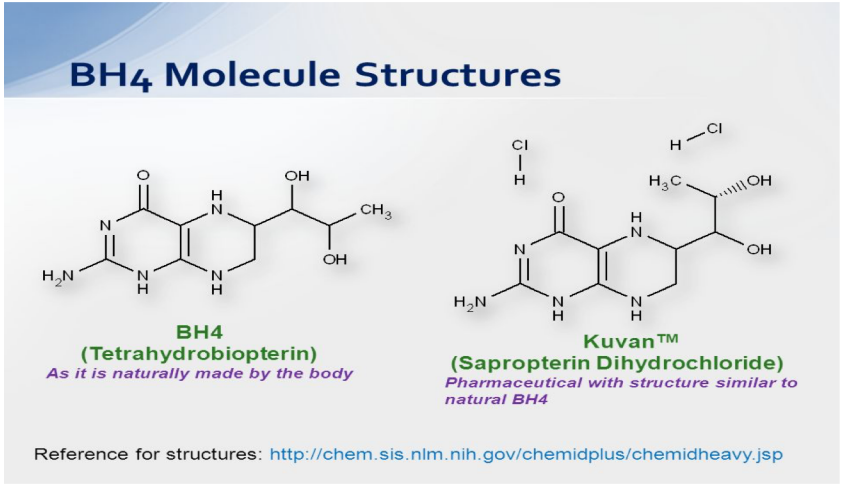
- The drug Kuvan® mimics BH4 which is a coenzyme/cofactor that assists PAH in the breakdown of Phe to Tyr.
- Kuvan® is not suitable for all patients who suffer PKU symptoms.
- How does Kuvan work?



Mechanism of action of Kuvan

Video file retrieved Feb 01, 2020 from

https://www.youtube.com/watch?v=62v-TuEBCFo

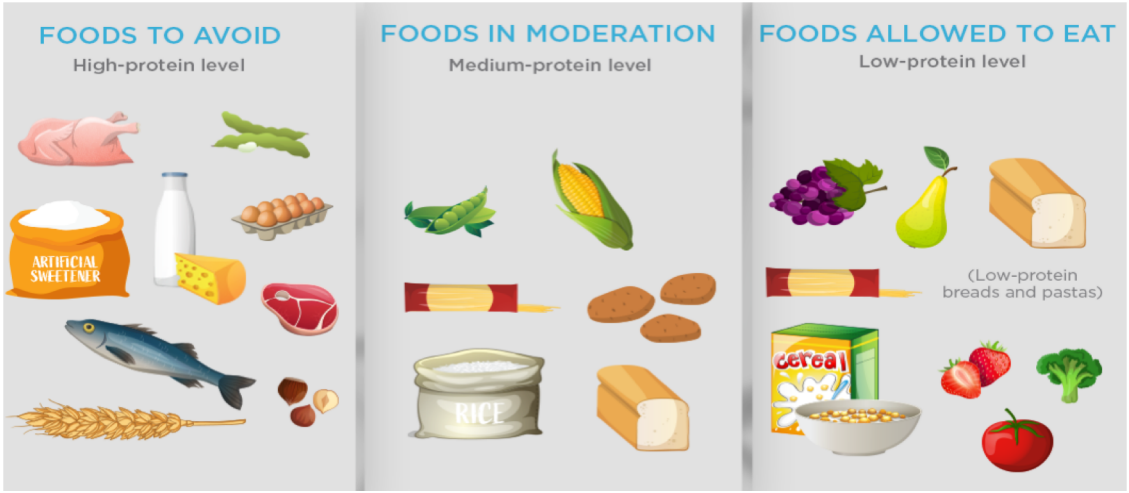


Digital image retrieved Oct 09, 2019 from

https://slideplayer.com/slide/7451969/

Therapy

- Treatment consists of a closely monitored diet
- Refrain from foods containing Phe and/or limit protein intake
- Pay close attention to aspartame-containing products (gum, diet soda, yogurt, etc.)



International PKU awareness day

Digital image retrieved Nov 13, 2019 from

https://www.nipd.com/articles/blog/international-phenylketonuria-awareness-day/

Importance of diet

- Careful dietary restriction is especially important for pregnant individuals with PKU or even non-PKU hyperphenylalanemia

- When there is a buildup of Phe in a pregnant mother, increased levels of Phe will cross the placenta, which has a detrimental effect on the developing fetus.
  - Craniofacial abnormalities, congenital heart disease, mental retardation, growth retardation
  - Fetus can display symptoms without having the PAH mutation

Available support

There are multiple agencies that support those affected:

➢National Organization for Rare Diseases (NORD)

Digital image retrieved Oct 16, 2019 from https://rarediseases.org/

- ➢ PKU & Me program (PKU.com)

Digital image retrieved Oct 14, 2019 from https://www.pku.com/community-and-support/pku-and-me

- ➢ The National PKU Alliance (npkua.org)
  - Dedicated to spreading awareness, and raising money for researching a cure.
  - Functions out of many clinics in Ohio including the Nationwide Children's Hospital in Columbus.

Digital image retrieved Oct 16, 2019 from https://www.npkua.org/

Phenylketonuria: Project team

Name	Project role
Tim Barley (Illustration)	Occurrence, Provenance, and Genetics
Maia Bates	Diagnosis and Symptoms
Jacob Brent	Additional Support
I. Rosemary Erwin (Text)	Therapy
Emma Montgomery	History
Cameron Spangler	Prognosis
Amanda Thornton	Biochemical Features

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